Advisory Committee Briefing Document for Safety with REMICADE®

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1.0 Introduction

REMICADE® (infliximab) is a monoclonal antibody that binds with high affinity and specificity to human tumor necrosis factor alpha (TNFα) and neutralizes its biologic activity. Clinical trials have demonstrated the efficacy of REMICADE in the treatment of both rheumatoid arthritis and Crohn's disease. REMICADE was approved in the US for the treatment of Crohn's disease in August 1998; for the treatment of signs and symptoms of rheumatoid arthritis (RA) in November 1999; and for the inhibition of structural damage due to RA in December 2000. REMICADE was approved in Europe for Crohn's disease in August 1999 and for signs and symptoms of RA in June 2000. An sBLA for improvement in physical function in RA was submitted to FDA in March 2001 (currently under review) and an sBLA is planned to be filed in third quarter 2001 for expanding the indication of REMICADE in patients with Crohn's disease.

Although the benefit:risk profile of REMICADE favors a strong benefit (as summarized in Section 5.0), some serious risks have been identified via postmarketing reports: opportunistic infections, most notably, tuberculosis. An effort has been underway at Centocor to characterize these risks and Centocor has worked closely with the FDA to modify the REMICADE label to communicate the known risks to Health Care Providers. Currently, Centocor is fortifying and extending its communication plans regarding the risk of TB, developing communications that will go to Health Care Providers as well as patients. In addition, Centocor has ongoing and planned clinical trials to collect data on known and potential risks with REMICADE administration. Finally, Centocor continues to collect long-term safety data on REMICADE-treated patients to better understand these risks.

This briefing document will describe the safety profile for REMICADE, the plans Centocor has for communicating safety issues both to physicians and patients, and the plans Centocor has for evaluating any future, potential safety risks and steps to be taken for reducing these risks.

2.0 Safety Data from Clinical Studies and Postmarketing Reports

To date, the safety of REMICADE has been assessed in 12 completed clinical trials, as well as 10 additional, recently completed, ongoing or partner-sponsored studies. Adverse event data have been pooled for the completed clinical studies and 2 ongoing studies in patients with Crohn's disease for which locked databases are available (a study in children through 20 weeks and a long-term, Phase III study [C0168T21; ACCENT I] through 30 weeks). This represents a cumulative database of 1514 patients' safety data; of these, 1372 received REMICADE. Two hundred two patients were treated with REMICADE for 2 years in the Phase III study in RA (C0168T22; ATTRACT).

As of June 30, 2001 an estimated 170,000 patients have been treated with commercial REMICADE worldwide since its first approval in 1998. This estimate is based on information of numbers of vials that have been sold, numbers of visits for infusions, and numbers of infusions per patient obtained from market sampling studies. These calculations assume all vial sales are attributed to either Crohn's disease or RA.

Clinical studies have explored doses of REMICADE ranging from 1 to 20 mg/kg. In patients with RA in the Phase III ATTRACT study, response rates tended to be higher at the 10 mg/kg dose, however, no additional structural damage benefit was seen compared with the 3 mg/kg dose. ATTRACT has demonstrated a lasting benefit with doses of at least 3 mg/kg.

2.1 Infections

The risk of infections observed with anti-TNF agents is most likely attributable to their mechanism of action. Anti-TNF agents neutralize the activity of tumor necrosis factor alpha (TNFα), which is an important mediator of inflammation and cellular immune responses. Published studies report that blockade of TNFα reduces host resistance to intracellular pathogens in animal models where endogenous TNFα is blocked with neutralizing antibodies (Flynn et al, 1995) or with soluble TNF receptors (Adams et al, 1995). The mechanism by which TNFα participates in host resistance is likely through its effects on macrophages and other phagocytic cells, including granuloma formation (Kindler et al, 1989). Thus, the blockade of TNFα may alter the normal granulomatous mechanisms for limiting the spread of infections.

Across all clinical studies and postmarketing surveillance, the majority of patients who have received REMICADE generally have severe underlying disease and as a consequence, are receiving immunosuppressants, including corticosteroids. Both the use of concomitant immunosuppressants and the severity of underlying inflammatory disease increases RA and Crohn's disease patients' predisposition to infections and other serious illnesses. Despite these facts, other than TB and opportunistic infections, serious

infections were not more frequent in REMICADE-treated patients than in patients who received placebo. Two deaths have occurred during clinical studies subsequent to a serious infection (1 due to disseminated TB and 1 to coccidioidomycosis).

Across all studies, the most frequent reported infection was upper respiratory tract infection, in 22.0% of infliximab-treated patients and 18.7% of placebo-treated patients. It should be emphasized that since follow-up for placebo patients was much shorter than for infliximab-treated patients, the reporting rates in placebo-treated patients may be artificially low. Other frequent (in > 5% of infliximab-treated patients) infections reported were sinusitis, pharyngitis, bronchitis, urinary tract infection, and moniliasis. All except bronchitis and urinary tract infection were reported slightly more frequently with infliximab than with placebo. However, in patients with Crohn's disease, pharyngitis and urinary tract infection were reported in slightly more placebo patients than infliximab-treated patients. Of note, sepsis occurred in similar, and low, proportions of patients treated with infliximab and placebo (1%) across all clinical trials.

Serious infections (ie, those that required or prolonged hospitalization) across all RA studies and all clinical studies are summarized in Table 1. Across all studies, the most frequent serious infection was pneumonia, reported in 0.9% of infliximab-treated patients and in 0.5% of placebo-treated patients. In general, the incidence of serious infections was low.

Table 1 Serious infections in clinical trials

	All RA Studies		All Studies	
	Placebo	Infliximab	Placebo	Infliximab
Pts treated	133	555	192	1372
Avg wks of follow-up	52	68	41	44
Pts with ≥ 1 serious infection	12 (9.0%)	45 (8.1%)	13 (6.7%)	56 (6.0%)
Pneumonia	1 (0.8%)	9 (1.6%)	1 (0.5%)	12 (0.9%)
Cellulitis	1 (0.8%)	6 (1.1%)	1 (0.5%)	7 (0.5%)
Skin ulceration	2 (1.5%)	4 (0.7%)	2 (1.0%)	4 (0.3%)
Sepsis	2 (1.5%)	4 (0.7%)	2 (1.0%)	6 (0.6%)
Infection bacterial	0 (0.0%)	3 (0.5%)	0 (0.0%)	4 (0.3%)
Arthritis	2 (1.5%)	2 (0.4%)	2 (1.0%)	2 (0.1%)
Bronchitis	0 (0.0%)	3 (0.5%)	0 (0.0%)	3 (0.2%)
Herpes zoster	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.2%)
Pyelonephritis	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.1%)

2.2 Tuberculosis

The risk of TB in patients with RA is complicated by several factors, such as their concomitant medications and where they live. The medications used for the therapy of RA are frequently immunosuppressive in nature. Prednisone at or above 15 mg daily for 1 month is considered to put patients at high risk for TB according to CDC guidelines (Centers for Disease Control and Prevention, 2000). Methotrexate, which is required concomitant treatment for all patients taking REMICADE for the treatment of RA is also considered to be immunosuppressive, although the dose of methotrexate that is considered to place patients at high risk for TB has not been established. In addition, combination therapy with corticosteroids and methotrexate is frequently given to patients with RA. The relative risk of the 2 drugs in combination has not been explored, but the combination may make patients more susceptible to reactivation of latent TB or to opportunistic infections, than either drug alone.

As of June 30, 2001 there have been 83 cases of active TB reported, with 80 from postmarketing surveillance and 3 from Centocor-sponsored clinical trials. These are

summarized by indication, seriousness, and geographic location in Table 2. Although the majority of the cases have been pulmonary, 25 cases (30.1%) have been disseminated. Other extrapulmonary sites were reported with lymph nodal presentation seen in 7 cases. Most patients treated with REMICADE for RA are also on concomitant methotrexate and, overall, the majority of patients were on at least 1 concomitant immunosuppressive agent.

Table 2 Summary of cumulatively reported postmarketing cases of tuberculosis

	Postmarketing Surveillance	Clinical Studies*	All Cases
Case totals (N)	80	3	83
No exposed (approximate)			
Age (years)	N = 69	N = 3	N = 72
Mean	53.1	63.0	53.5
Minimum	18.0	N/A	18.0
Maximum	83.0	N/A	83.0
Age distribution (N, %)	N = 69	N = 3	N = 72
≤ 35	13 (18.8%)	0 (0.0%)	13 (18.1%)
36-50	18 (26.1%)	0 (0.0%)	18 (25.0%)
51-65	18 (26.1%)	3 (100.0%)	21 (29.2%)
66-80	19 (27.5%)	0 (0.0%)	19 (26.4%)
≥ 81	1 (1.4%)	0 (0.0%)	1 (1.4%)
Gender (N, %)	N = 73	N = 3	N = 76
Male	25 (34.2%)	1 (33.3%)	26 (34.2%)
Female	48 (65.8%)	2 (66.7%)	50 (65.8%)
Indication (N, %)	N = 74	N = 3	N = 77
CD	19 (25.7%)	1 (33.3%)	20 (26.0%)
RA	50 (67.6%)	2 (66.7%)	52 (67.5%)
Other	5 (6.8%)	0 (0.0%)	5 (6.5%)
Seriousness (N, %)	N = 80	N = 3	N = 83
Fatal	12 (15.0%)	2 (66.7%)	14 (16.9%)
Life threatening	2 (2.5%)	1 (33.3%)	3 (3.6%)
Hospitalization	52 (65.0%)	1 (33.3%)	53 (63.9%)
Disability	1 (1.3%)	0 (0.0%)	1 (1.2%)
IME	40 (50.0%)	1 (33.3%)	41 (49.4%)
Non-serious	10 (12.5%)	0 (0.0%)	10 (12.0%)
Geographical origin (N, %)	N = 80	N = 3	N = 83
EU/Norway/Other	58 (72.5%)	1 (33.3%)	59 (71.1%)
North America	22 (27.5%)	2 (66.7%)	24 (28.9%)

* The Clinical Studies column includes the PROMPT trial (a Phase IIIb trial).
CD = Crohn's disease
EU = European Union
HCP = health care provider
IME = important medical event
N = number

Of interest is the timing of the diagnosis of TB in patients treated with REMICADE. When infusion number was known, the vast majority (97%) of cases presented within the first 6 infusions of REMICADE, with 75% within the first 3 infusions, usually within 6 months of starting REMICADE therapy. The timing of onset, soon after the initiation of REMICADE therapy, suggests that the active infection may be a result of reactivation of latent TB.

Specific countries and relative numbers of TB cases reported for REMICADE in Europe are shown in Figure 1 (upper panel), which demonstrates that the greatest number of cases occur in southern Europe (Spain, France, and Italy). Figure 1 (lower panel) shows the distribution of REMICADE use in those countries. Note that cases in the US were not localized in any 1 area (Figure 2).

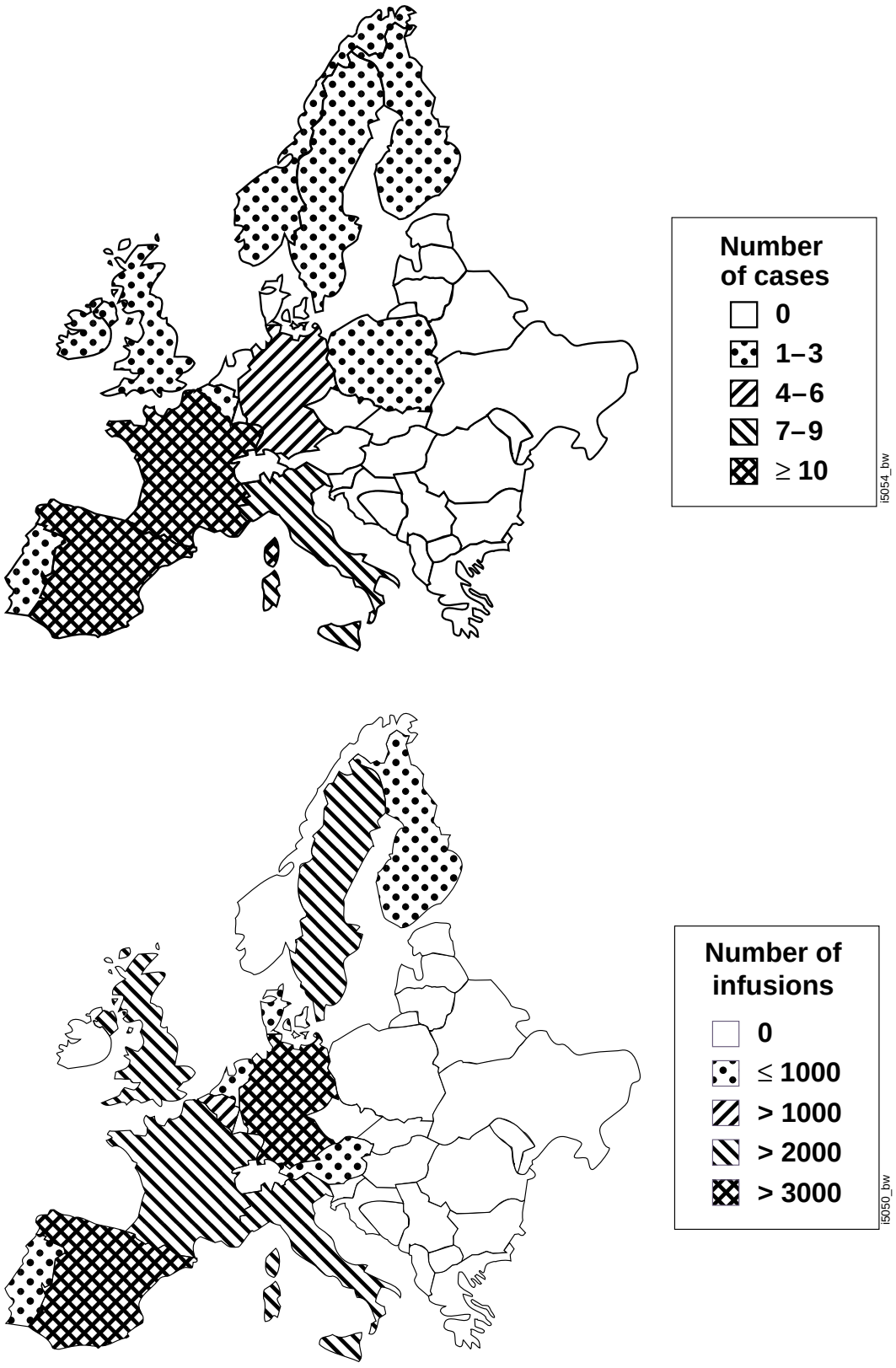

Figure 1 Number of cases of TB and pattern of use of REMICADE in Europe

Figure 2 Cases of TB in the US through June 30, 2001
Two cases were reported in Seattle.

On October 6, 2000, Centocor and Schering Plough (Centocor's corporate partner for the sales and marketing of REMICADE outside the US [except the Far East]) brought together a consortium of worldwide infectious disease experts from the United States, England, France, Spain, Italy, South Africa, South America, and Malaysia to discuss the rate of TB infection in REMICADE-treated patients and the proper precautionary measures to be taken for diagnosis and treatment of TB.

The overall conclusions reached by the expert panel were as follows:

- Incidence: TB incidence rates vary with age, geographic location, etc. The incidence of latent TB in Europe is much higher than the US. Although incidence rates of TB are available for the general population, there are no official incidence records maintained for patients who have Crohn's disease or RA. Given the degree of background immunosuppression and other risk factors in REMICADE-treated patients, it is not possible to determine the magnitude of the risk for TB in REMICADE patients.

- Timing: The fact that the cases occurred within 6 months of REMICADE dosing was of interest. The limited information reported confounded the interpretation of the data. The general consensus was that a possibility exists that there could be a

temporal association between initiating REMICADE therapy and onset of the TB. The timing of the cases suggested reactivation of latent TB.

- Presentation: More patients than expected presented with disseminated TB. It was believed that such presentations were unusual and indicated that the patients were immunocompromised.

- Guidelines: Standard guidelines exist in caring for patients who are or will be immunocompromised through the administration of any immunomodulatory agent. These guidelines should be used for the targeted patient population of RA and Crohn's disease for which REMICADE is indicated. In the US, the CDC guidelines are explicit that screening with PPD skin tests should be carried out in all high-risk patients, which would include patients considering REMICADE therapy.

  - Local guidelines for screening for TB should be followed in countries outside the US.

  - For the targeted REMICADE patient population who are at risk of developing active TB infection such as those with positive PPD or recent close contact with an infected family member, standard TB prophylaxis therapy should be initiated concurrently with REMICADE therapy.

  - In countries where TB is endemic, the consensus was that no additional precautions beyond those in the guidelines were necessary.

- Follow-up: To determine if an increased incidence or risk is associated with REMICADE, the following possible studies could be considered: patient registries, other post-marketing surveillance techniques and/or epidemiological case controlled studies.

2.3 Opportunistic Infections

As of June 30, 2001 a number of fungal and other opportunistic infections have occurred in patients receiving REMICADE. Most patients who developed these infections were receiving concomitant immunosuppressive agents including corticosteroids, methotrexate, azathioprine, cyclophosphamide and others. Histoplasmosis (9 cases) occurred only in areas of the US in which this infection is endemic (the Mississippi and Ohio River Valleys); 1 patient with histoplasmosis died. Pneumocystis carinii (12 cases), arose mostly in patients receiving concurrent immunosuppressive therapies; 3 patients with PCP died. Eight cases of listeria were identified (4 were in North America and 4 in Europe/Norway); 2 patients with listeria died. Aspergillosis (6 cases), developed mostly in the setting of severe immunosuppression, with 3 of the 6 known cases occurring in patients receiving REMICADE (off label) for the treatment of graft vs host disease (GVHD). Three patients with aspergillosis died. Systemic candidiasis (7 cases), occurred in patients who had in common either the presence of a central line or

pronounced concurrent immunosuppression; 3 patients with candidiasis died. Cryptococcosis was reported in 2 patients (no deaths). Coccidioidomycosis occurred in 2 patients (1 disseminated and the patient died, and 1 septic joint).

A teleconference was held with histoplasmosis experts George Deepe, MD, and L Joseph Wheat, MD, to discuss any steps to be taken to reduce the risk of histoplasmosis infection. The experts concluded the following:

1. There is no skin test available for screening patients for exposure to histoplasmosis;
2. Serological tests for histoplasmosis are not reliable or practical;
3. Prophylaxis for patients in endemic areas is not appropriate;
4. The appropriate management of patients who reside in areas endemic for histoplasmosis who are receiving REMICADE is:
    - Careful benefit:risk assessment prior to treatment
    - Careful monitoring of patients while on therapy

2.4 Blood Dyscrasias

Through 30 June 2001, in completed and ongoing studies, the only blood dyscrasias of note were 1 (blinded) case of pancytopenia in a patient with RA and 1 (blinded) in a patient with Crohn's disease. In the postmarketing database, 15 cases of pancytopenia were identified in patients with RA (5, 61.5%) and Crohn's disease (8, 38.5%). Considering the low incidence and frequent association with the use of concomitant immunosuppressants, there does not appear to be an increased risk for this event with REMICADE administration.

2.5 Demyelinating Disorders/Neuropathies

Through 30 June 2001, 9 cases of central demyelination (3 relapses of pre-existing multiple sclerosis, 3 cases of multiple sclerosis, 1 optic neuritis with positive oligoclonal banding, 1 progressive multifocal leukoencephalopathy, and 1 unknown). In addition, 4 cases of optic neuritis, and 6 cases of Guillain Barré Syndrome/chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have now been reported. Additionally, there were 30 medically confirmed reports of neuropathy, 17 (61%) of which occurred in patients with Crohn's disease. It should be noted that the majority of peripheral neuropathies were reported in patients with Crohn's disease, which is not surprising since peripheral neuropathies are more common with Crohn's disease, in part due to malabsorption of vitamin B12 as a result of terminal ileal disease (Agranoff and Schon, 1995). While the reported incidence is low, continued surveillance and assessment of individual cases is ongoing.

2.6 Summary

Overall, the safety profile of REMICADE continues to be favorable. Appropriate concern regarding the incidence of infection has been noted, especially with regard to the development of active TB. Screening of patients for TB in clinical studies has been mandated and appropriate screening and prophylactic management have been recommended in the current approved labeling for the product. At this time there does not appear to be an association of REMICADE with either demyelinating diseases or with pancytopenia, although monitoring of these events continues.

3.0 Labeling Changes to Address Safety Findings

In December 2000, Centocor updated and strengthened the "Warnings" section of the REMICADE package insert, based on ongoing safety information collected by Centocor and discussed with the FDA. In addition, at that time, the indication for RA was expanded to include inhibiting the progression of structural damage in patients with moderately to severely active RA who have had an inadequate response to methotrexate. The following are changes of note to the safety sections:

Warnings - The "Risk of Infections" bolded section was expanded to include the cases of tuberculosis (including disseminated tuberculosis) and noted that "patients should be evaluated for the risk of tuberculosis, including latent tuberculosis" and that "treatment for tuberculosis should be initiated prior to treatment with REMICADE." The Warnings section was expanded to also include information that anti-TNF agents have been associated with exacerbation of demyelinating disease.

Centocor also disseminated this safety information via a letter to Health Care Professionals issued by Centocor's Sales and Marketing Department (issued January 5, 2001). The letter summarized the known incidence of TB in REMICADE patients and recommended that patients be evaluated for the risk of TB prior to treatment with REMICADE.

Centocor and the FDA are currently in discussions to update the labeling for REMICADE based on new postmarketing and clinical data obtained since the last labeling revision. At the time of this document (July 23, 2001) the final labeling has not been approved.

4.0 Risk Management Program

4.1 Introduction

Centocor has developed a communication plan for both patients and prescribers that focuses on TB, to build awareness of the risk of TB, and the diagnosis, treatment, and monitoring of TB in patients receiving REMICADE. This plan, as well as descriptions of ongoing and planned studies to further assess the incidence of infections in a variety of clinical settings, are described in this section. Methods for monitoring the rate of infections are detailed below.

4.2 Communication Plan

Figure 3 outlines the schedule for the extensive communication plan to be rolled out by Centocor. The sections below describe the plan outlined in Figure 3.

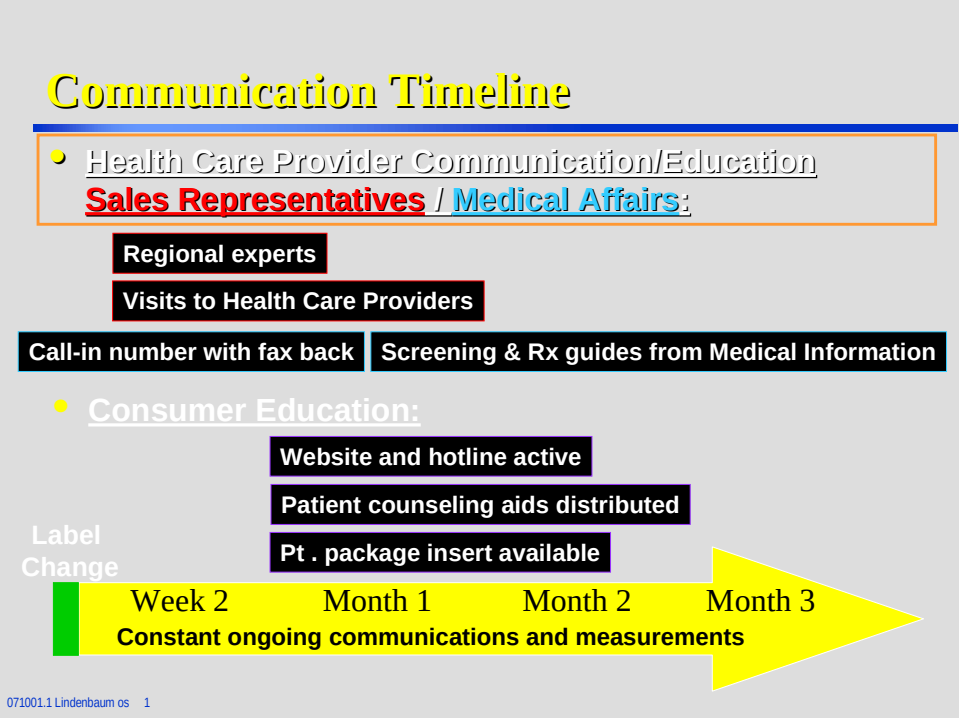

Figure 3 Communication timeline

4.2.1 Field Force

Currently, Centocor has a sales force of 273 immunology specialists (approximately 1 representative for every 30 prescribing physicians) and other field-based representatives who regularly interact with physicians treating patients with RA and Crohn's disease. In addition, there are 29 field-based Medical Affairs personnel (Clinical Information Scientists) who will undergo a training program overseen by Centocor's Medical Affairs Department. The program will consist of detailed information on the background of TB; the role of TNF; screening procedures for TB; diagnosis procedures; and treatment procedures for both latent and active TB. Nine of these 29 individuals will serve as primary instructors in the etiology, epidemiology, appropriate screening, test result interpretation, treatment options, and responses to frequently asked questions concerning TB.

All field-based personnel will be trained in the field, tested, and required to show a ≥ 90% proficiency in the safety course material. Additionally, all basic Centocor training materials will be updated. Finally, updated information will be distributed to the 29 Clinical Information Scientists, and to the rest of the Field Force, on an as-needed basis.

4.2.2 Health Care Providers

As for the Field Force, information on TB, TNF, and the screening and treatment of TB will be prepared for professionals who treat patients. This will be done via several mechanisms:

- Field representatives will visit physicians and provide information with clear, physician-oriented guidelines on precautions prior to and during treatment with REMICADE. This will include materials for ongoing treatment of current patients; how to screen patients for TB; and recommendations from leading authorities on the treatment for TB such as the CDC and American Thoracic Society. Field representatives will also provide health care providers with a Patient Leaflet, a new-start patient counseling guide, and a current-patient counseling guide. Currently available promotional literature will be updated or revised in accordance with FDA-proscribed timelines.

- A call-in number will be ready with guidelines for the diagnosis and treatment of TB, as well as information on how to acquire and administer PPD tests.

- Medical information letters will be updated with current TB information and will be made available through our web site.

- "Dear Health Care Professional" letters will be mailed to the entire prescribing audience, approximately 15,000 individuals.

- The REMICADE web site, which currently exists and is geared both to patients and prescribers, will have updated information on the risk of infections and, specifically, TB, soon after the approval of the package insert. The web site will also have links to other web sites that will have more detailed information on TB. The Centocor web site will be updated on a regular basis, with late-breaking information.

4.2.3 Patients

In order to gather the most appropriate information for patients who receive REMICADE, and to focus information for both patients and physicians, Centocor plans to evaluate and define the patient population who are being treated with REMICADE. This will be carried out through collaborative identification through the offices of REMICADE-treated patients and through feedback from REMICADE-treated patients who choose to participate in Centocor's patient compliance program.

Information concerning the risk of TB with REMICADE treatment will also be available for patients, as follows:

- The REMICADE web site, mentioned above.

- Patients considering REMICADE therapy who have called the REMICADE information hotline will receive updated information. This will include information addressing the potential safety issues and side effects of REMICADE.

- Patients already being treated with REMICADE who contact the information hotline will receive our current patient counseling guide.

- In addition, patients will receive a Patient Leaflet, which is in its final stages of development.

4.2.4 Measurement of Communication Plan Effectiveness

The effectiveness of the communication plan described above will be evaluated, using 2 methods:

1. Based on the target audience, health care provider call records will be tabulated with a "call counting" program. The Centocor Sales Department and Medical Affairs Department will count, until September 1, 2001 the number of physicians receiving safety details and the date of visit.

2. Quantitative and qualitative research methods will be used to track physician understanding of, and suggested actions to, the label change.

4.3 Ongoing and Planned Clinical Studies to Evaluate Safety

Ongoing studies (including approximately 1500 REMICADE-treated patients) and planned studies (including registries) are described below. Overall, Centocor plans to follow approximately 15,000 patients prospectively for the incidence of infections.

4.3.1 Ongoing Phase II and III Studies

Currently, Centocor is conducting 1 Phase III trial in patients with Crohn's disease, 1 Phase III trial in patients with RA, and 1 Phase II trial in patients with congestive heart disease. Other clinical Phase II or III trials in psoriasis, juvenile RA, and ulcerative colitis will begin in the near future.

4.3.2 Phase IIIb and IV Studies

4.3.2.1 PROMPT Study

The PROMPT (Profiling REMICADE Onset with Methotrexate in a Prospective Trial) study was a multicenter, open-label, Phase IIIb study of 553 patients enrolled at 80 sites. Patients received 3 mg/kg REMICADE at weeks 0, 2, 6, 14, 22, and 30. The objectives of this study, which was completed in February 2001, were to determine the onset of efficacy of REMICADE and to further establish the safety of REMICADE given in the office. The safety endpoints from this trial were consistent with other REMICADE experiences.

4.3.2.2 RA Safety Study (START)

The START (Safety Trial for Rheumatoid Arthritis with REMICADE Therapy) trial is a 1-year, 1000-patient, placebo-controlled trial that will be performed in a population of patients with RA that is reflective of patients treated in clinical practice. All patients will be on background methotrexate and have active disease, defined as 6 swollen and 6 tender joints. The inclusion and exclusion criteria have been relaxed to enroll patients with chronic illnesses, including chronic renal failure and certain chronic infections such as hepatitis C. Patients may be on a variety of other DMARDs for the treatment of RA including cyclosporine.

Two doses of REMICADE will be compared to placebo through 22 weeks. The primary endpoint will be the number of serious infections at any time through week 22 and will estimate an upper limit of the 95% confidence limit for the relative risk of serious infection in the combined REMICADE-treated groups. The trial is powered at 80%, at a 5% significance level to rule out a two-fold increase in serious infections based on the assumption that the rate is the same between the experimental and placebo groups.

After 22 weeks, patients in the placebo group will cross over to REMICADE at 3 mg/kg every 8 weeks for the remainder of the 52 weeks of the trial.

Issues:

Patient population: Although designed to broaden the demographics of the population from that seen in clinical trials, the population selected by the START trial may still not be truly representative of the population of patients being treated in the community. Importantly, since REMICADE is now commercially available and there are multiple ongoing clinical trials for a variety of agents, the START trial is likely to be populated with patients who do not have access to REMICADE commercially and who do not qualify for other clinical trials. Such selection may provide demographics that are actually at higher risk for complications than the population normally treated in the community. Therefore, the placebo group is necessary for at least the first 22 weeks but interpretation of complications following the controlled portion of the trial will be difficult to interpret.

Study size: The size of the study is large enough to detect a two-fold increase in serious infections at week 22. Little information is expected to be obtained regarding individual, less frequent events such as TB (both because of the low incidence and the fact that screening for latent TB will be performed) or opportunistic infections (again due to low incidence).

4.3.2.3 IRAMT Study

The planned enrollment for this IRAMT (Infliximab Rheumatoid Arthritis Methotrexate-Tapering protocol) study is 200 patients. This is an open-label study in which all patients will receive REMICADE with methotrexate. The objective of this trial is to monitor the safety, tolerability, and efficacy of REMICADE with methotrexate when the methotrexate dose is tapered to a minimum of 5 mg/week. Patients will begin to taper methotrexate once they have achieved a 40% improvement in clinical signs and symptoms following the initiation of REMICADE therapy.

4.3.3 Registries

Postmarketing registry studies are currently underway, to gather additional safety information for patients with RA and Crohn's disease.

The TREAT (Therapy Research Evaluation and Assessment Tool) program is evaluating outcomes in patients with Crohn's disease in both community and academic practices. For this program, Centocor has assembled an advisory panel consisting of world leaders in the research and management of Crohn's disease. This panel has reviewed and endorsed the scientific and ethical foundation of the registry. The goal of this registry, which began in August 1999, is to enroll 200 physicians and from 3,000 to 5,000 patients. This registry collects clinical, safety, and quality-of-life outcomes associated with Crohn's disease treatment for 2 to 5 years. Patients who are receiving and not receiving REMICADE are included.

The Wolfe registry is enrolling patients from a typical practice of medicine setting referred to as the REMICADE Rheumatoid Arthritis Registry. As the program sponsor, Centocor works with the National Data Bank for Rheumatic Diseases to collect data and conduct in-depth analyses. This registry, which began in January 2001, has a projected enrollment of 5,000 patients. Clinical, safety, and quality-of-life outcomes associated with REMICADE treatment will be tracked and analyzed. Patient response cards are being collected every 6 months and data analyzed semi-annually. Dr. Wolfe's data bank will also enable generation of control groups that can be matched to the group of patients receiving REMICADE.

4.3.4 Long-term Safety Follow-up for REMICADE Studies

All patients enrolled in any REMICADE Phase I, II, or III study will be enrolled in a long-term safety follow-up protocol which will collect information for at least 3 years. The objective of this follow-up is to collect information on the long-term safety of REMICADE with respect to major safety events (ie, deaths, serious infections, malignancies, and new autoimmune disorders).

4.3.5 Case-controlled Study of TB after REMICADE Exposure

A case-controlled study will be performed to determine what factors identify the REMICADE-treated patients who are at greatest risk for TB, based on a case-controlled study described by Strom et al (1989). The study population will be US and non-US REMICADE-exposed patients from the practices that spontaneously reported active TB after REMICADE use.

All REMICADE-exposed patients who, as of the study survey date, were the subject of adverse event (AE) reports indicating active TB, will be evaluated. Spontaneous and study AE reports will be included. For each case, up to 4 controls will be selected. These will be selected from REMICADE-exposed patients in the same medical practice who did not have TB reported.

Patients known to have active TB at the time they first received REMICADE will be excluded from the study but patients with a history of TB will not be excluded.

Data will be analyzed as a matched case-controlled study with a variable number of controls per case (ranging from 1 to 4 depending on availability). Cases with no controls will be excluded from the analysis. Analysis will be directed toward identifying the factors associated with case status, eg, age, sex, race, type of medical insurance, medications (REMICADE and others), past exposure to TB, and past treatment of TB (for those who were exposed).

4.4 Summary of Planned Studies

As shown in Table 3, 9 studies will be conducted to better characterize safety and risks with REMICADE. The studies will enroll approximately 15,000 patients.

Table 3 Current and planned REMICADE studies

Study	No. of Patients	Status
ASPIRE	1050	Ongoing
ACCENT I & II	779	Ongoing
PROMPT	553	Completed
ATTACH	150	Ongoing
IRAMT	200	Planned
START	1000	Planned
TREAT	5000	Ongoing
Wolfe	5000	Ongoing
Long-term safety follow-up	1050	Ongoing
Total	Approximately 15,000	

5.0 Summary and Conclusions

5.1 Sponsor's Benefit and Risk Assessment

5.1.1 Benefit

The efficacy of REMICADE was evaluated in patients with RA in 4 placebo-controlled trials and 2 open-label trials. As is currently indicated, in patients with an inadequate response to MTX, REMICADE, in combination with MTX, has been shown to rapidly relieve the signs and symptoms of RA and to inhibit the progression of structural damage in patients with active RA. Data through 102 weeks in C0168T22 (ATTRACT) confirmed that these benefits are accompanied by improvement in physical function, thereby fulfilling an important unmet medical need (data currently under FDA review).

The efficacy of REMICADE for active RA in patients, who have had an inadequate response to methotrexate, was clearly demonstrated in clinical trials, specifically:

- REMICADE provided a consistent, durable, clinically and statistically significant benefit by inhibiting the progression of structural damage, with regard to both erosions and joint space narrowing, a benefit that no other therapy has demonstrated.

- REMICADE provided a consistent, durable, clinically and statistically significant benefit by reducing the signs and symptoms of RA, and REMICADE provided a major clinical response (ie, an ACR 70% response for 6 consecutive months) in a significantly greater proportion of patients than with placebo.

- REMICADE has also demonstrated a consistent, durable, clinically and statistically significant benefit by improving physical function, a benefit for which no therapy is currently indicated. This data was submitted in March 2001 and is currently under FDA review.

The efficacy of REMICADE in Crohn's disease has been clearly demonstrated in clinical trials, specifically:

- REMICADE reduced clinical signs and symptoms and produced clinical remission in patients with active Crohn's disease who are not responding to corticosteroid therapy, a benefit for which no other therapy is indicated.

- REMICADE has been shown to allow Crohn's disease patients to have their corticosteroid therapy reduced or withdrawn in a recently completed trial (C0168T21). This data will be submitted to FDA for review.

5.1.2 Risk

The safety of REMICADE has been assessed in 12 completed clinical trials, as well as 10 additional recently completed, ongoing or partner-sponsored studies. In addition, information from postmarketing surveillance on greater than 170,000 patients treated with REMICADE has been analyzed. Several risks have been consistently identified and other areas of concern are noted as a result of information available from other anti-TNF agents.

- Infections, including TB and other opportunistic infections and sepsis, have been observed with REMICADE therapy, although in clinical studies, serious infections were not more frequent in REMICADE-treated patients than in patients who received placebo.

- Acute infusion reactions (including anaphylaxis) and delayed hypersensitivity (serum sickness-like) reactions have been observed with REMICADE infusions, although serious infusion reactions were uncommon in clinical trials and during postmarketing surveillance.

- Although the development of autoantibodies has been observed in some patients, the risk of autoimmune disease (including lupus-like syndrome) is low.

- Malignancies (including lymphoma), demyelinating disease, and blood disorders (including pancytopenia) have been observed in extremely low numbers of patients following treatment with REMICADE, although the risk of these events with REMICADE therapy is uncertain. Malignancies, demyelinating disease, hematologic events are continuing to be monitored.

5.2 Conclusions

While a risk of infections is to be expected with any immunomodulating agent, including anti-TNF products, the risk of serious and opportunistic infections in patients receiving REMICADE appears to be somewhat higher. In particular, patients receiving REMICADE may be at higher risk for reactivation of latent TB. The association between REMICADE and opportunistic infections is difficult to assess since the patients typically taking REMICADE have other risk factors; however, Centocor is performing or planning to perform several studies to better characterize this risk. Similarly, the relationship between REMICADE and other events (demyelinating disorders/neuropathies, blood disorders, malignancies), is, at this point, difficult to determine.

Centocor has undertaken a multi-faceted approach to communicate the risks of developing TB while on REMICADE, as well as guidelines for targeted tuberculin testing and treatment of latent TB infection. The communication plan includes ongoing education programs for health care providers and patients, and includes measures to assess the effectiveness of the communication.

Overall, the risk of TB appears to be small and, if the guidelines communicated by Centocor are followed, largely preventable. The risk management program proposed by Centocor should result in a decrease in the reporting rate of TB in patients receiving REMICADE.

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